Modelling and monitoring of the freeze-drying process

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# Modelling and monitoring of the freeze-drying process

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Freeze drying, or lyophilization, is the process whereby a solvent (generally water) is removed by sublimation from a frozen material, usually under the condition of low pressure and continuously providing heat in order to compensate the energy absorbed during sublimation. Lyophilisation is known to be both slow and expensive because slow drying rates and the use of vacuum are involved. Furthermore, the interactions in the variables of the freeze-drying process are complex, and an experimental approach to the study of the various operational policies is tedious, expensive and time-consuming. Thus, by means of theoretical modelling the correlation between the process variables has been investigated in the objective to use it in the complex tasks of design, optimization, and control.

A detailed transient mathematical model for freeze-drying in vial has been developed and translated into a numerical code in order to predict the spatial and time evolution of the product temperature and of the position of the moving front that originates during the sublimation process. A transient energy balance, which never was taken into account in previously published models, has been introduced, describing heat transfer along the glass of the vial sidewall. The model has been validated with experimental data obtained in a pilot freeze-drier giving a good agreement. The detailed model has proven to give very good predictions of the dynamics of the primary drying phase of the process, but the number of variables involved and the complexity of the mathematical formulation prevent it to be used in a supervision or control strategy for the process. Thus, a simplified pseudo-steady state model, suitable for real-time monitoring and control purposes, has been developed providing explicit analytical expressions for the temperature profiles inside the vial.

The obtained mathematical laws were used for synthesising a non-linear observer, or soft-sensor. An observer is a tool which can give on-line information on non-measurable or hard to measure process variables, combining a priori knowledge about the physical system (mathematical model) with the experimental data coming from physical sensors (on-line measurements). The most important parameter to be monitored and controlled during primary drying is the temperature of the product, because sublimation must be carried out in the frozen state at a controlled temperature, in order to avoid denaturation of the product. However, it is well known that the presence of a thermocouple inside the vial can alter the freezing process, and consequently the final drying time. Thus, it appeared as an interesting approach to realise a soft-sensor capable to monitor the product temperature starting from the non-invasive measure of the vial sidewall temperature. The performances of the observer were tested with data obtained with the detailed transient model. When starting from good initial conditions, the developed soft-sensor proved to be able to follow the dynamics of the product temperature all along the sublimation phase. As a possible application, this kind of observer could be inserted in a control loop in order to control the temperature of the product at a target value, compatible with the denaturation limit of the material.

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